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APPLICANT:	Christopher T. Boyle	ATTORNEY DOCKET:	6006-018
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TITLE: DEVICE FOR IN VIVO DELIVERY OF BIOACTIVE AGENTS AND METHODS OF MAKING SAME

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Lori Dunham

AMENDMENT AFTER ALLOWANCE

Dear Sir:

Please consider the following Amendment under 37 C.F.R. §1.312. The issue fee has not been paid.

Claims listing begins on page 2 of this paper.

Amendments to the Specification begin on page 5 of this paper.

Replacement Sheets are attached to this paper.

Remarks begin on page 13 of this paper.

Claims listing

Claim 16: (Currently Amended) An endoluminal stent for delivering a bioactive agent to a situs in a body, comprising:

a plurality of vacuum deposited structural elements forming a radially expandable cylindrical member, the plurality of vacuum deposited structural ~~vacuum deposited~~ elements including a complex finished geometry, each of the plurality of vacuum deposited structural elements having a wall thickness; wherein the vacuum deposited structural elements are fabricated of a metal and comprise a base layer and a second layer covering the base layer, further comprising a void space intermediate the base and second layers that is enclosed therebetween;

a plurality of pores passing through the second layer and communicating with the void space such that the void space is open only through the plurality of pores; and

at least one bioactive agent retained within the void space and elutable through the plurality of pores.

Claim 20: (Previously Presented) The endoluminal stent according to claim 16, further comprising a degradable plug residing within the plurality of pores to prohibit release of the at least one bioactive agent until the degradation of the degradable plug.

Claim 26: (Previously Amended) The endoluminal stent according to claim 16, wherein the metal is selected from the group consisting of titanium, vanadium, aluminum, nickel, tantalum, zirconium, chromium, silver, gold, silicon, magnesium, niobium, scandium, platinum, cobalt, palladium, manganese, molybdenum and alloys thereof, including zirconium-titanium-tantalum alloys, nitinol, and stainless steel.

Claim 27: (Previously Presented) The endoluminal stent according to claim 16, wherein the bioactive agent further comprises a pharmacologically active agent selected from the group consisting of antibiotic drugs, antiviral drugs, neoplastic agents, steroids, fibronectin, anti-clotting drugs, anti-platelet function drugs, drugs which prevent smooth muscle cell growth on inner surface wall of vessel, heparin, heparin fragments, aspirin, coumadin, tissue plasminogen activator, urokinase, hirudin, streptokinase, antiproliferatives, methotrexate, cisplatin, fluorouracil, adriamycin, antioxidants, ascorbic acid, beta carotene, vitamin E, antimetabolites, thromboxane inhibitors, non-steroidal and steroidal anti-inflammatory drugs, immunosuppresents, such as rapomycin, beta and calcium channel blockers, genetic materials including DNA and RNA fragments, complete expression genes, antibodies, lymphokines, growth factors, vascular endothelial growth factor and fibroblast growth factor, prostaglandins, leukotrienes, laminin, elastin, collagen, nitric oxide, and integrins.

Claim 28: (Previously Presented) The endoluminal stent according to claim 16, wherein the void space comprises a plurality of independent internal cavities along the length of the structural elements.

Claim 30: (Previously Presented) The endoluminal stent according to claim 16, wherein the metal of the first and second layers has at least one surface thereof having controlled heterogeneities thereupon.

Claim 31: (Previously Presented) The endoluminal stent according to claim 30, wherein the controlled heterogeneities are selected from the group consisting of grain size, grain phase, grain material composition and surface topography.

Claim 32: (Previously Presented) The endoluminal stent according to Claim 30, wherein the controlled heterogeneities define polar and non-polar binding sites for binding blood plasma proteins.

Claim 33: (Currently Amended) The endoluminal stent according to Claim 30, wherein the controlled heterogeneities are dimensioned to have a blood contact surface area substantially similar in size [[as]] to endothelial cell surface integrin clusters.

Claim 34: (Previously Presented) The endoluminal stent according to Claim 30, wherein the controlled heterogeneities define cell-adhesion domains having interdomain boundaries less than the surface area of a human endothelial cell.

Claim 35: (Previously Presented) The endoluminal stent according to Claim 30, wherein the controlled heterogeneities form binding domains having a repeating pattern with no more than about 2 μm border to border spacing between adjacent binding domains.

Claim 36: (Previously Presented) The endoluminal stent according to Claim 30, wherein the controlled heterogeneities are dimensioned to have a blood contact surface area of about less than 6 μm^2.

Claim 37: (Currently Amended) The endoluminal stent according to Claim 30, wherein the controlled ~~heterogeneity has~~ heterogeneities have a blood contact surface less than or equal to about 10 μm and an inter-heterogeneity boundary between about 0 and 2 μm.

Amendments to the Specification

Replace the paragraph beginning on page 1 line 23 and ending on page 2 line 9 with the amended paragraph as follows:

Occlusive diseases, disorders or trauma cause patent body lumens to narrow and restrict the flow or passage of fluid or materials through the body lumen. One example of occlusive disease is arteriosclerosis in which portions of blood vessels become occluded by the gradual build-up of arteriosclerotic plaque.[[,]] [[t]]This process is also known as stenosis. When vascular stenosis results in the functional occlusion of a blood vessel the vessel must be returned to its patent condition. Conventional therapies for treatment of occluded body lumens include dilatation of the body lumen using bioactive agents, such as tissue plasminogen activator (TPA) or vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) gene transfers which have improved blood flow and collateral development in ischemic limb and myocardium (S. Yla-Herttuala, *Cardiovascular gene therapy*, Lancet, Jan 15, 2000), surgical intervention to remove the blockage, replacement of the blocked segment with a new segment of endogenous or exogenous graft tissue, or the use of a catheter-mounted device such as a balloon catheter to dilate the body lumen or an artherectomy catheter to remove occlusive material. The dilation of a blood vessel with a balloon catheter is called percutaneous transluminal angioplasty. During angioplasty, a balloon catheter in a deflated state is inserted within an occluded segment of a blood vessel and is inflated and deflated a number of times to expand the vessel. Due to the inflation of the balloon catheter, the plaque formed on the vessel walls cracks and the vessel expands to allow increased blood flow through the vessel.

Replace the paragraph beginning on page 3 line 1 and ending on page 3 line 29 with the amended paragraph as follows:

It has been found desirable to deliver bioactive agents to the area where a stent is placed concurrently with stent implantation. Many stents have been designed to deliver[[y]] bioactive agents to the anatomical region of stent implantation. Some of these stents are biodegradable stents which are impregnated with bioactive agents. Examples of biodegradable impregnated stents are those found in U.S. Pat. Nos. 5,500,013, 5,429,634, and 5,443,458. Other known bioactive agent delivery stents include a stent disclosed in U.S. Pat. No. 5,342,348 in which a bioactive agent is impregnated into filaments which are woven into or laminated onto a stent.

U.S. Pat. No. 5,234,456 discloses a hydrophilic stent ~~that may include a bioactive agent adsorbed~~ which can include a biologically active agent disposed within the hydrophilic material of the stent. Other bioactive agent delivery stents are disclosed in U.S. Pat. Nos. 5,201,778, 5,282,823, 5,383,927; 5,383,928, 5,423,885, 5,441,515, 5,443,496, 5,449,382, 4,464,450, and European Patent Application No. 0 528 039. Other devices for endoluminal delivery of bioactive agents are disclosed in U.S. Pat. Nos. 3,797,485, 4,203,442, 4,309,776, 4,479,796, 5,002,661, 5,062,829, 5,180,366, 5,295,962, 5,304,121, 5,421,826, and International Application No. WO 94/18906. A directional release bioactive agent stent is disclosed in U.S. Patent No. 6,071,305 in which a stent is formed of a helical member that has a groove in the abluminal surface of the helical member. A bioactive agent is loaded into the groove prior to endoluminal delivery and the bioactive agent is therefore in direct apposition to the tissue that the bioactive agent treats. Finally, International Application No. WO 00/18327 discloses a drug delivery stent in which a tubular conduit is wound into a helical stent. The tubular conduit has either a single continuous lumen or dual continuous lumens that extend the entire length of the conduit. The tubular conduit has regions or segments thereof that [[has]] have pores to permit drug "seepage" from the conduit. One end of the tubular conduit is in fluid flow communication with a fluid delivery catheter, which introduces a fluid, such as a drug, into the continuous lumen and through the pores. Where biodegradable or non-biodegradable polymer-based or polymer-coated stents have been used, the polymers cause an immune inflammatory response once the drug is eluted out of the polymer. Where a polymer is employed as the bioactive agent carrier, it is, therefore, desirable to isolate the polymer from body tissues in order to limit the immune inflammatory response after the bioactive agent has eluted as can be accomplished with the present invention.

Replace the paragraph beginning on page 5 line 1 and ending on page 5 line 6 with the amended paragraph as follows:

The inventive stent for delivery of bioactive agents consists generally of a plurality of structural elements, at least some of which have internal cavities that retain the bioactive agents, and openings that pass between the internal cavities and the surface of the structural elements to communicate the bioactive agent from the internal cavity to external the stent. Other than described herein, the present invention does not depend upon the particular geometry, material, material properties or configuration of the stent.

Replace the paragraph beginning on page 6 line 22 and ending on page 7 line 2 with the amended paragraph as follows:

With particular reference to Figure 1, the present invention consists generally of a body element 10 having a three-dimensional conformation defining X, Y and Z-axes of the body element 10 and at least one of a plurality of interior cavities 12 defined within the body element 10, and at least one of a plurality of passages or pores 14 which communicate between the at least one of a plurality of interior cavities 12 and exterior to the body element 10. While the body element 10 depicted in Figure 1 is of a generally cylindrical three dimensional conformation, alternative three dimensional conformations, such as planar, spherical, ovular, tetrahedral, curvilinear or virtually any other three dimensional conformation suitable for implantation into a living body [[is]]are contemplated by the present invention. The plurality of passages 14 have dimensions sufficient to permit the bioactive agent to elute by diffusion, osmotic pressure or under the influence of a positive pressure applied by cellular in-growth into the plurality of interior cavities 12.

Replace the paragraph beginning on page 7 line 3 and ending on page 7 line 21 with the amended paragraph as follows:

The location of the plurality of passages 14 is dependent upon the particular application for which the body element 10 is intended. For example, with particular reference to Figures 2-[[5]]4, where the body element 10 is a tubular body 20 made of a plurality of interconnected structural elements 21, such as a stent, stent-graft or graft, which defines a central lumen 22 and has openings 24 at opposing proximal and distal ends of the tubular body 20, the plurality of passages 14 are formed in at least some of the plurality of interconnected structural elements 21 and may be disposed on only the luminal surface 26 or only on the abluminal surface 28 of the tubular body 20, or both. Pores 14 on the luminal surface 26 only will communicate the bioactive agent into the lumen 22 and any body fluid, such as blood, flowing through the central lumen 22 of the tubular body 20, while pores 14 on only the abluminal surface [[26]]28 will communicate the bioactive agent to the abluminal surface 28 of the tubular body 20. At least a portion of some of the plurality of interior cavities 12 may communicate with either the proximal or distal ends of at least some of the plurality of interconnected structural elements 21. In this

case, the proximal and/or distal ends of at least some of the plurality of interconnected structural elements 21 may be tapered such as to be self-cannulating into body tissue during delivery and deployment. The bioactive agent retained within the internal cavity 12 which communicates with the proximal and/or distal ends of at least some of the plurality of interconnected structural elements 21 will then pass out of the proximal and/or distal ends in much the same manner as fluid flowing through an injection needle.

Replace the paragraph beginning on page 7 line 22 and ending on page 8 line 16 with the amended paragraph as follows:

In addition to the foregoing positioning of the pores 14, both the plurality of internal cavities 12 and the plurality of pores 14 may be positioned to be discontinuous and in different circumferential or different longitudinal regions of the tubular body 20. Within a single one of the plurality of interconnected structural elements 21, the internal cavities 12 may be separated by a separation member 25, which completely subtends the internal cavity 12, ~~divides~~ dividing it into discrete discontinuous internal cavities 12. The advantage of forming a plurality of discontinuous internal cavities 12 is that it permits loading of different bioactive agents into different regions of the body member 10 or tubular member 20 to isolate different regions for delivery of different bioactive agents to different sites within a body. For example, a first grouping of a plurality of internal cavities 12 and associated plurality of pores 14 may be located at a proximal end of the tubular body 20, and a second grouping of a plurality of internal cavities 12 and associated plurality of pores 14 may be located at an intermediate region of the tubular body 20, and a third grouping of a plurality of internal cavities 12 and associated plurality of pores 14 may be located at a distal end of the tubular body 20. A first bioactive agent may be loaded into the first and third groupings of a plurality of internal cavities 12, while a second bioactive agent may be loaded into the second grouping of a plurality of internal cavities 12. Where, for example, the tubular body 20 is an endoluminal stent, stent-graft or graft which is implanted post-angioplasty, the proximal and distal ends of the tubular body 20 are anchored adjacent to healthy tissue while the intermediate region of the tubular body 20 [[are]] is positioned adjacent to the diseased or injured tissue. In this configuration, a first bioactive agent, such as an endothelial growth factor and/or contrast medium to impart enhanced ~~radioopacity~~ radiopacity to the tubular body 20 may be carried in the first and third groups of a plurality of

internal cavities 12 and associated pores 14, while an anticoagulant, such as heparin, may be carried in the second grouping of a plurality of internal cavities 12 and associated pores 14. In this manner, the tubular body has enhanced ~~radioopacity~~ radiopacity to aid in delivery and deployment and endothelial growth factors to enhance endothelialization of the tubular body 20, while delivering an anticoagulant directly to the site of the tissue lesion.

Replace the paragraph beginning on page 8 line 17 and ending on page 8 line 22 with the amended paragraph as follows:

Moreover, where the internal cavities 12 are discontinuous, the plurality of pores 14 may be configured to include degradable plugs which degrade at different rates to expose different bioactive agents in the internal cavities 12 to the body at different points in time. Alternatively or additionally, the degradable plugs may degrade at different rates to expose the same bioactive agent in different internal cavities 12 at different periods of time to effectively elongate the period of time during which the bioactive agent is delivered.

Replace the paragraph beginning on page 8 line 27 and ending on page 9 line 7 with the amended paragraph as follows:

Turning to Figures 5-7 there is illustrated an alternative embodiment of the inventive endoluminal stent 30 fabricated from a plurality of tubular structural elements 31 formed into a tubular stent and having a desired geometry. It will be appreciated that the generally hexagonal cell geometric pattern defining a plurality of interstices 32 as illustrated in Figure 5 is merely exemplary and a myriad of different geometries of different geometric complexities are contemplated by the invention. Each of the tubular structural elements 31 has a central lumen [[37]] that forms the internal cavity 37 within each structural element 31. A plurality of separation members 38 may be provided to subdivide the internal cavity 37 into a plurality of discontinuous internal cavities 37. Each of the tubular structural elements 31 has a plurality of openings 36 which communicate between the internal cavity 37 and one or both of a luminal surface 33 or an abluminal surface 35 of each of the plurality of tubular structural elements 31. The tubular structural elements 31 may assume any transverse cross-sectional configuration having a central lumen.

Replace the paragraph beginning on page 9 line 8 and ending on page 9 line 14 with the amended paragraph as follows:

Those of ordinary skill in the stent forming arts will understand that in order to form a tubular endoluminal stent 30 of tubular elements 31, it is necessary to join at least some of the plurality of tubular elements 31. Conventionally, a plurality of spot-welds 34 ~~which~~ serve to interconnect sections of individual tubular elements 31 in juxtaposed relationship to one and other. The plurality of spot welds 34 may also be employed to seal the internal cavity 37 at the position of the spot weld, thereby creating a separation member 38 within the internal cavity 37 of each individual tubular element 31 and forming [[a]] discontinuous internal ~~cavity~~ cavities 37.

Replace the paragraph beginning on page 9 line 15 and ending on page 9 line 28 with the amended paragraph as follows:

As noted above, the plurality of openings 36 are dimensioned to permit the bioactive agent to elute from the at least one of a plurality of internal cavities 37 and through the associated plurality of openings 36 by diffusion, osmotic pressure or under the influence of a positive pressure applied by cellular in-growth into the plurality of internal cavities 37 or under positive pressure applied by stress and/or strain exerted on the plurality of internal cavities 37 due to deformation of the individual tubular structural elements 31. Additionally, the positioning of the plurality of openings 36 relative to the individual tubular structural elements 31 and to the endoluminal stent 30 as a whole may be adapted to deliver varying quantities of or different bioactive agents from different regions of the tubular structural elements 31 or different regions of the endoluminal stent 30. Moreover, proximal and/or distal ends of individual tubular structural elements 31 may be tapered so as to form self-cannulating ends of the individual tubular structural elements 31 which penetrate body tissue and permit the bioactive agent to be communicated from the internal cavity 37 out the proximal or distal end of the tubular structural element 31 in a manner similar to a hypodermic needle.

Replace the paragraph beginning on page 9 line 29 and ending on page 10 line 7 with the amended paragraph as follows:

In accordance with another embodiment of the present invention, and as illustrated in Figures 8-10, there is provided an implantable device 40 which consists of a structural body 42

having a three-dimensional conformation extending in the X-axis, Y-axis and Z-axis ~~dimensionally~~ dimensions. While the illustrated embodiment of the structural body 42 is planar, those of ordinary skill in the medical device fabrication art will understand that it is within the skill of the artisan to fabricate the structural body 42 of any desired three-dimensional conformation depending upon the desired use and indication of the implantable device 40. The three-dimensional conformation of the structural body 42 may be cylindrical, tubular, quadrilinear, planar, spherical, ovular, tetrahedral, curvilinear or virtually any other three-dimensional conformation suitable for implantation into a living body.

Replace the paragraph beginning on page 10 line 16 and ending on page 11 line 13 with the amended paragraph as follows:

Each of the above-described preferred embodiments of the present invention may be fabricated by a number of methods. In accordance with present invention, it is contemplated that forming the implantable devices by vacuum deposition techniques [[are]] is the preferred method of making the implantable structural elements of the present invention. Where an implantable device is to be fabricated of a plurality of individual tubular elements, such as depicted in Figures 5-7, pre-existing microtubular members having an outer diameter, for example, between 60 and 400 μm and a wall thickness of between 10 and 350 μm, may be employed to fabricate extremely small dimensioned devices suitable for intracranial or coronary artery applications. The microtubular members may be formed into a cylindrical endoluminal device, such as by braiding or bending and joining microtubular members together by spot welding. Where ends of the microtubular members are formed to be self-cannulating, the self-cannulating ends may be exposed on the abluminal surface of an endoluminal device at any point along the longitudinal axis thereof. The plurality of openings passing through the wall of each of the individual tubular elements may be formed by microdrilling the openings through the wall and into the internal cavity or lumen of the individual tubular members. The plurality of openings may be laser cut, etched or formed by EDM methods, and may be formed either pre- or post- formation of the tubular elements into the three-dimensional conformation of the implantable device. Where an implantable device is to be formed from non-preexisting structural elements, vacuum deposition techniques may be employed to form the implantable structural body, such as sputtering, reactive ion etching, chemical vapor deposition, plasma vapor deposition, or the like, as are known in the

microelectronics fabrication arts and are more fully described in co-pending, commonly assigned U.S. Patent Application Serial No. 09/443,929, filed November 19, 1999, which is hereby incorporated by reference. Because, the internal cavities and openings must be formed during deposition, the vacuum deposition techniques must be modified to deposit requisite patterns of sacrificial material to form the regions of the internal cavities and openings, over a base layer of structural material, then depositing a second layer of structural material over the sacrificial material and the base layer. The sacrificial material may then be removed, such as by etching, to leave the internal cavities and plurality of openings formed within the deposited bulk material.

Replace the paragraph beginning on page 11 line 14 and ending on page 11 line 25 with the amended paragraph as follows:

Regardless of which fabrication method is employed, the bioactive agent must be loaded into the internal cavities of the implantable device. Loading of the bioactive agent may be accomplished by flowing a liquid or semi-liquid state of the bioactive agent through the plurality of openings and into the internal cavities, either throughout the entire device or in regions of the implantable device. Flow loading may be facilitated by applying positive pressure, temperature change or both, such as is used in hot isostatic pressing (HIP). In HIP the pressurizing medium is typically a gas, and the process is carried out at elevated temperatures for specific time periods. While HIP is typically utilized to densify materials, to heal casting defects and voids, or to bond similar or dissimilar materials it may be used to drive a fluid or semi-fluid from external the implantable device into the internal cavities of the implantable device. Alternatively, diffusion-mediated loading, osmotic loading or vacuum loading may be employed to load the bioactive agent into the internal cavities.

Remarks

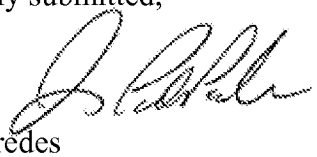
The Applicant submits an amendment under 37 C.F.R. §1.312 to amend Claims 16, 33, and 37. The claim amendments resolve inadvertent typographical issues in the method claims. These amendments do not impact the scope of any of the claims, and are intended merely to correct informalities. Support for the amendments may be found throughout the originally filed specification. The Amendments are needed for proper protection of the invention, require no substantial amount of additional work on the part of the Office, and require no further search or examination on the Examiner's part. As such, the amendments do not require the application to be withdrawn from allowance or issuance for proper entry.

The Amendments to the Specification are to correct for inadvertent typographical errors and correct reference numerals. No new matter has been entered and the Amendments are needed for proper protection of the invention and require no substantial amount of additional work on the part of the Office. The Applicant also submits Replacement Sheets for Figures 2, 9, and 10 to correct reference numerals. For Figure 2, Replacement Sheet 1 replaces incorrect reference numerals 24 with correct reference to structural elements 21. Replacement Sheet 3 replaces incorrect reference numerals 49 with correct reference to the lateral surface 45 in Figures 9 and 10. The applicant respectfully requests entry of the same.

Fees and Deposit Account

No fee is believed due with the filing of this document, however, in the event the U.S. Patent and Trademark Office determines that other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this documents to Deposit Account No. 18-2000, of which the undersigned is an authorized signatory.

Respectfully submitted,



J. Peter Paredes
Reg. No. 57,364

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ROSENBAUM & SILVERT, P.C.
1480 Techny Road
Northbrook, IL 60062
Tel: (847) 770-6000
Fax: (847) 770-6006

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